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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/920,033	08/01/2001	Rosanne M. Crooke	ISPH-0592	5785

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EXAMINER	
EPPS FORD, JANET L	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 06/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/920,033	CROOKE ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,5,8-13,15-20 and 28-39* is/are pending in the application.

4a) Of the above claim(s) *15-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-5, 8-13, 20, 28-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 4-7-06
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4-07-06 has been entered.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

3. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

4. Claims 1, 4-5, 8-13, 20, 28, 29-34, and 36-38 are rejected under 35 U.S.C. 102(a or e) as being anticipated by Bennett et al. (US Patent No. 6172216, Published January 9, 2001).

5. Bennett et al. discloses an antisense oligonucleotide 20 nucleobases in length (SEQ ID NO: 22), wherein said antisense oligonucleotide comprises 13 identical nucleobases with SEQ ID NO: 247 of the instant application. SEQ ID NO: 22 of Bennett et al. comprises a region of 9 contiguous nucleobases that are 100% complementary to nucleobases 3258-3268 of SEQ ID NO: 3 of the instant application.

ISIS No. 16000, see col. 29, Table 3, has the sequence as set forth in the antisense oligonucleotide of SEQ ID NO: 22 (as described above), wherein said antisense oligonucleotide is a chimeric oligonucleotide, comprising wherein positions 1-5 and 16-20 comprise a 2'-MOE modification (other positions comprise 2'-deoxy modifications), all 2'-MOE cytosine residues are 5-methylcytosines, and all linkages are phosphorothioate linkages.

Bennett et al. also teach wherein the antisense compounds of their invention comprise sodium salts, see for example, col. 11, lines 14-23. Additionally, the invention of Bennett et al. also includes compositions comprising the disclosed antisense compounds in combination with a pharmaceutically acceptable carrier or diluent, see col. 14. Moreover, Bennett et al. teach that regardless of the method by which the antisense compounds of the invention are introduced into a patient, colloidal dispersion systems may be used as delivery vehicles to enhance the in vivo stability of the compounds and/or to target the compounds to a particular organ, tissue or cell type.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1, 4-5, 8-13, 20, 28, 29, 31, 33-34, and 36-38 are rejected under 35 U.S.C. 102(b) as being anticipated by Baker et al. (WO 00/00504 A1).

Baker et al. discloses antisense oligonucleotide ISIS#-19479 (SEQ ID NO: 24), this sequence is 18 base pairs in length and is 88.9% complementary to nucleotides 177 through 194 of SEQ ID NO: 3 of the instant application (see Table 2, page 54). This antisense oligonucleotide is a chimeric oligonucleotide, comprising wherein positions 1-4 and 15-18 comprise a 2'-MOE modification (other positions comprise 2'-deoxy modifications), all 2'-MOE cytosine residues are 5-methylcytosines, and all linkages are phosphorothioate linkages.

Baker et al. also discloses pharmaceutical formulations, and compositions comprising the antisense compounds of their invention in a colloidal dispersion system, see pages 27-28. Moreover, Baker et al. also teach pharmaceutically acceptable salts of the disclosed antisense compounds, including sodium salts, see bridging paragraph of pages 19-20.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1, 4-5, 8-13, 20, 28, 29-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bennett et al. as applied above, in view of Wengel et al. (US 2002/0068708A1).

11. The discussion of Bennett et al. as set forth above is incorporated here, however, Bennett et al. do not teach the incorporation of bicyclic modified sugar bases into the structure of their disclosed antisense compounds.

Wengel et al. provides a review of the benefits of designing oligonucleotide compounds to comprise Locked Nucleic Acid bicyclic sugar modifications. According to Wengel et al., oligonucleotides comprising this class of sugar modification are able to

provide valuable improvements to oligonucleotides with respect to affinity and specificity towards complementary RNA and DNA oligomers (see abstract and page 3).

It would have been obvious to the ordinary skilled artisan at the time of the instant invention to modify the antisense compounds of Bennett et al. to comprise bicyclic nucleoside monomers (LNA). One of ordinary skill in the art at the time of the instant invention would have been motivated to make this modification since the prior art teaches that antisense compounds comprising LNA modifications produces antisense compounds with stability towards exonucleolytic degradation, effective delivery into cells, and display unprecedented binding affinity to both RNA and DNA (see Wengel et al., page 1, paragraph [0014]).

12. Claims 1, 4-5, 8-13, 20, 28-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rouy et al. (US Patent No. 6,512,161; or WO 99/35241 A1; see IDS of 4-07-06; citations given for US Patent), and Eggerman et al. (See IDS of 4-06-05) in view of GenBank Accession No NM_000384 (Huang et al. Reference #1), Monia et al. (US 5,656,612; see Reference A of PTO-892 mailed 1/14/2003), Agrawal et al. (2000, see Reference U of PTO-892 mailed 1-13-2004), and Wengel et al. (US 2002/0068708A1).

Rouy et al. teach the following at col. 12, lines 5-25:

> The down regulation of gene expression using antisense nucleic acids can be achieved at the translational or transcriptional level. Antisense nucleic acids of the invention are preferably nucleic acid fragments capable of specifically hybridizing with a nucleic acid encoding apolipoprotein (a) or B or the corresponding messenger RNAs. These antisense nucleic acids can be synthetic oligonucleotides, optionally modified to improve their stability and selectivity. They can also be DNA sequences whose expression in the cell produces RNA complementary to all or part of the mRNA encoding apolipoprotein (a) or B. Antisense nucleic acids can be prepared by

expression of all or part of a nucleic acid encoding apolipoprotein (a) or B, in the opposite orientation, as described in EP 140308. Any length of antisense sequence is suitable for practice of the invention so long as it is capable of down-regulating or blocking expression of apolipoprotein (a) or B. Preferably, the antisense sequence is at least 20 nucleotides in length.

Eggerman et al. demonstrate that antisense oligonucleotides targeted for apoB decreased apoB mRNA expression in human liver cell lines by up to 80%.

However, Rouy et al. and Eggerman et al. do not disclose non-catalytic compounds of 12 to 30 nucleobases in length that specifically hybridize to the nucleotide sequence set forth in SEQ ID NO: 3, or specifically to nucleotides 1 to 103 or 157-14121 of SEQ ID NO: 3 and demonstrates at least 70% reduction of the apolipoprotein B mRNA levels when applied *in vitro* at a concentration of 150 nM to HepG2 cells.

Additionally, Rouy et al. and Eggerman et al. do not disclose said non-catalytic compounds comprising the various modifications recited in the instant claims, or compositions thereof.

GenBank Accession No. NM_000384 discloses the 14121 base pair nucleotide sequence encoding the full-length sequence of apolipoprotein B. The sequence report indicates that the coding sequence has a start codon at nucleotide 129. Comments on pages 4-5 of the report indicate that apolipoprotein B has two isoforms the intestinal apoB-48 and hepatic apoB-100, these two forms are coded by a single gene and by a single mRNA transcript, wherein the smaller form is postulated to be the result of an organ specific RNA editing process.

Monia et al. describe methods for the modulation of expression of the human ras

oncogene in a cell comprising the administration of modified antisense oligonucleotides. The oligonucleotides used in the methods of Monia et al. are preferably chimeric oligonucleotides that contain two or more chemically distinct regions, each made up of at least one nucleotide. These oligonucleotides typically contain at least one region of modified nucleotides that confers one or more beneficial properties (such as, for example, increased nuclease resistance, increased uptake into cells, increased binding affinity for the RNA target) and a region that is a substrate for enzymes capable of cleaving RNA: DNA or RNA: RNA hybrids (col. 6, lines 49-67). The modified antisense oligonucleotides used in the *in vitro* inhibition methods of Monia et al. may comprise phosphorothioate internucleoside modifications, a 5-methylcytosine modified nucleobase, and may further comprise 2'-methoxyethoxy sugar modifications (col. 7-8). The antisense oligonucleotide modifications disclosed by Monia et al. have been shown to increase both binding affinity of the oligonucleotide for its target and nuclease resistance of the oligonucleotide (col. 6, lines 45-58). Furthermore, Monia et al. teach the use of pharmaceutical carriers to facilitate the uptake of oligonucleotides into cells. These carriers include: ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Compositions for oral administration include powders or granules, suspensions or solutions in water or non-aqueous media, capsules, sachets, or tablets. Thickeners, flavorings, diluents, emulsifiers, dispersing aids or binders may be desirable. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable. Coated condoms, gloves and the like may also be useful, cationic lipids may be included in the formulation to facilitate

oligonucleotide uptake (col. 7, lines 40-67).

Agrawal et al. provides motivation for designing antisense oligonucleotides targeting various regions of a target mRNA, including for example the coding region and the 5'-UTR and 3'-UTR of a target mRNA. According to Agrawal et al. "[I]t is considered preferable, therefore, to screen a number of oligonucleotides that encompass different regions on RNA to identify a set of optimal target sites, including the 5'- and 3'-untranslated regions (UTRs), initiation codon site, coding region and intron-exon junctions." (page 77, 1st para.) Additionally, Agrawal et al. generally states (regarding the feasibility of utilizing antisense technology), "antisense technology has become an essential laboratory tool to study and understand the function of any newly discovered genes in recent years."

Wengel et al. provides a review of the benefits of designing oligonucleotide compounds to comprise Locked Nucleic Acid bicyclic sugar modifications. According to Wengel et al., oligonucleotides comprising this class of sugar modification are able to provide valuable improvements to oligonucleotides with respect to affinity and specificity towards complementary RNA and DNA oligomers (see page 1, paragraph [0014]).

It would have been obvious to one of ordinary skill in the art, at the time of the instant invention, to modify the teachings of Rouy et al. and Eggerman et al. with the teachings of GenBank Accession No. NM_000384, Monia et al., Agrawal et al., and Wengel et al. to design non-catalytic oligonucleotides compounds of 12 to 30 nucleobases in length, that specifically hybridizes to the nucleotide sequence set forth in SEQ ID NO:3, excluding the start codon region, and further modifying the

oligonucleotides with one or more sugar modifications, internucleoside linkage modifications, and nucleobase modifications.

One of ordinary skill in the art would have been motivated to design compounds of 12 to 30 nucleobases in length since Rouy et al. expressly teaches antisense oligonucleotides targeting apolipoprotein B mRNA comprising at least 20 nucleobases in length. Moreover, one of ordinary skill in the art would have been motivated to design oligonucleotide compounds targeting apolipoprotein B mRNA comprising one or more sugar modifications, phosphorothioate modified internucleoside linkages, and 5'-methylcytosine modified nucleobases, since Monia et al. teaches that these modifications are known to both increase hybridization efficiency and nuclease resistance of oligonucleotide compounds comprising these modifications. Moreover, Monia et al. teach that oligonucleotides comprising these modifications possess a high target site specificity and increased cellular uptake in comparison to unmodified antisense oligonucleotides. Furthermore, one of ordinary skill in the art at the time of the instant invention would have been motivated to make this modification since the prior art teaches that antisense compounds comprising LNA modifications produces antisense compounds with stability towards exonucleolytic degradation, effective delivery into cells, and display unprecedented binding affinity to both RNA and DNA (see Wengel et al., page 3, lines 25-35).

Additionally, one of ordinary skill in the art seeking to further understand the role of apolipoprotein B gene expression in cellular processes, would have been motivated to design antisense oligonucleotides targeting the mRNA encoding the apolipoprotein B

gene as defined by SEQ ID NO: 3 of the instant specification, since GenBank Accession No. NM_000384 clearly set forth the nucleotide sequence of SEQ ID NO: 3 as the sequence encoding the full-length apolipoprotein B mRNA. Moreover, NM_000384 clearly defines the 5'-UTR as occurring before nucleotide 129, start codon region as beginning at nucleotide 129, and the coding sequence as extending from nucleotide 129 to nucleotide 13820, therefore the 3' UTR would be defined as the remaining sequence corresponding to nucleotides 13821 through 14121. Moreover, according to Agrawal et al., if the nucleotide sequence of a gene was known, designing antisense oligonucleotides to target the various regions of that gene, including the 5' UTR, the coding sequence and the 3' UTR (see above description of Agrawal et al.) that would allow the ordinary skilled artisan to further elucidate the role of that gene of interest in various cellular processes.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Janet L. Epps-Ford, Ph. D.
Primary Examiner
Art Unit 1633

JLE